EXHIBIT A

PAUL J. MICHAELS, M.D.

BOARD CERTIFIED IN ANATOMIC AND CLINICAL PATHOLOGY, AND CYTOPATHOLOGY

Expert Report of Paul J. Michaels, M.D.
(Re: General Opinions)

BACKGROUND:

I am certified by the American Board of Pathology in Anatomic Pathology, Clinical Pathology, and Cytopathology. I attended and received my medical degree from the University of California, Los Angeles School of Medicine. I completed a residency in anatomic and clinical pathology at Massachusetts General Hospital, an affiliate of the Harvard School of Medicine, where I was a Clinical Fellow in Pathology. Following my residency, I completed a year of subspecialization in Cytopathology, also at Massachusetts General Hospital.

I am a pathologist affiliated with Clinical Pathology Associates in Austin, Texas. I have staff privileges at University Medical Center at Brackenridge, Seton Medical Center Austin, St. David's Medical Center, Seton Northwest Hospital, Seton Southwest Hospital, Seton Highland Lakes Hospital, Dell Children's Medical Center of Central Texas, Arise Austin Medical Center, Westlake Medical Center, Central Texas Medical Center (San Marcos, TX), and Resolute Health Hospital (New Braunfels, TX). Presently, I am the Laboratory Director for two separate Stat clinical laboratories in the Austin area, both affiliated with Clinical Pathology Laboratory/Sonic Healthcare USA, the third largest pathology company in the United States. During my career, I have had a strong subspecialty focus in breast and gynecology pathology, as well as cytopathology. I regularly attend and participate in tumor multidisciplinary conferences. In addition, I was a contracted speaker with Genomic Health, Inc., specializing in the Onco*type* DX Breast Cancer Assay. I was also an invited speaker at the annual National Interdisciplinary Breast Center Conference for the National Consortium of Breast Centers, both in 2012 and 2013, lecturing on various topics in the field of breast cancer. My current curriculum vitae is attached to this report.

I have been asked to provide an expert report regarding my general opinions as they relate to this litigation. In preparation for providing this opinion, I have reviewed numerous studies published in the scientific literature, as well as various Ethicon documents, deposition testimony, and other materials in arriving at my findings and opinions in this matter, a list of which is attached to my report. All of my opinions stated below are held to a reasonable degree of medical and scientific certainty and I reserve the right to modify or change my opinions based on further documents or information that may be provided to me in the future.

COMMENT:

Not long after the commencement of transvaginal mesh (TVM) repair for POP and SUI, many complications were reported as being directly related to sequela from the host response of the implanted synthetic graft. The most common complications included mesh erosion and extrusion of the mesh through the vagina, pain, bleeding, secondary infection, dyspareunia, urinary problems, partner pain, and even organ fistula formation. Many of these complications required repeat surgical intervention. The pathologic response to the synthetic grafts used in surgery depends in large part on the physical and structural properties of the prosthesis. This host response varies based on mesh absorbability, pore size (size between filaments), and overall weight/density.

While absorbable material initially elicits a chronic foreign body inflammatory reaction, following complete absorption and subsequent fibroblast proliferation, the material is replaced by collagen-rich connective tissue, devoid of most acute or chronic inflammatory elements with obvious resolution of any foreign body reaction (Klinge 1999; Klinge 2001). In contrast, non-absorbable prosthetic material such as polypropylene is typically characterized by a persistent inflammatory response with ongoing foreign body-type giant cells (tissue macrophages), chronic inflammatory cells, and neovascularization. A study of modified mesh material used experimentally in a surgical setting that contained a mixture of non-absorbable polypropylene and absorbable polyglactin showed that reducing the amount of polypropylene (non-absorbable) to less than 30%, though still providing the necessary mechanical stability, significantly reduced the degree of inflammation and subsequent fibrosis, leading to increased mesh flexibility (Klinge 1998). In a separate experimental study in dogs, also by Klinge and colleagues (1998), a multifilament combination of nonabsorbable polypropylene and absorbable polyglactin histologically showed considerably less inflammation and stromal fibrosis, compared to monofilament polypropylene grafts.

Studies over many years have uniformly supported the finding that larger mesh pore sizes have better incorporation into the surrounding native tissues (Greca 2001; Klinge 2002; Weyhe 2006). Whereas smaller pore sizes significantly impair vessel and adipose tissue penetration secondary to prominent fibrosis between adjacent mesh filaments (“bridging fibrosis”) (Chvapil 1969; Klinge 1999; Klinge 2002; Klosterhalfen 2005; Cobb 2006), larger-pore mesh material allows for infiltration by vascularized connective fibroadipose tissue (Taylor 1972; Cobb 2015) both structurally allowing for reduced fibrosis with subsequent retention of flexibility (Orenstein 2012; Lake 2015) and decreasing the ability for infection by bacteria introduced into the surgical site at the time of implantation (Merrit 1979). Additionally, the foreign body-type giant cell response and prominent fibrosis invariably encasing small pore meshes often forms a capsule surrounding the whole mesh (“scar plate”), resulting in the mesh becoming stiff, contracted, and nonflexible (Klosterhalfen 2005). Therefore, mesh contraction is defined

by the reduction in surface area of the original implanted graft due to a retraction of the fibrotic scar tissue around the mesh.

Meshes with larger pore size generally have less material per square unit of measurement and are therefore of a lower weight, whereas those with smaller pore sizes are heavier. Analogous to the data showing a favorable host response with large pore size mesh, studies have concluded that light weight synthetic mesh shows better tissue integration with less inflammation and scar fibrosis (Klinge 1999; Klinge 2002; Klosterhalfen 2005), while the extent of stiffness increased directly in relationship to mesh weight (Cobb 2006).

In addition to the above described histological tissue responses and morphological modifications to implanted synthetic graft material, the clinical symptom of pain has become a significant postoperative complication in surgical cases using polypropylene mesh. The etiology of postsurgical pain can obviously be multifactorial, and several authors have evaluated the clinical consequence of pain in the context of patients with mesh grafts. In some instances, the marked mesh contraction secondary to bridging fibrosis and scar plate formation leads to erosion through the vaginal wall with a resulting acute inflammatory response, triggering regional pain.

Inflammation is a complex tissue reaction to injurious agents resulting in vascular responses, migration and activation of leukocytes, and, occasionally, systemic consequences. Inflammation is divided into acute and chronic patterns.

Acute inflammation has three major components including alteration in vascular caliber and blood flow, structural changes in the microvasculature that permit plasma proteins and leukocytes to leave the circulation, and emigration of leukocytes, mainly neutrophils, from the microcirculation to the focus of injury. Acute inflammatory reactions can be triggered by a variety of stimuli, including foreign bodies. Vasodilation is one of the principle manifestations of acute inflammation which results in increased blood flow that often manifests as an area of increased heat and redness. Clinically, these features not infrequently lead to a complaint of pain at the site of increased blood flow.

Classically, the presence of neutrophils is the hallmark of acute inflammation within tissue. Once neutrophils have migrated from the vascular space into the tissue, they become activated leading to the production of arachidonic acid metabolites, degranulation and secretion of lysosomal enzymes, activation of the oxidative burst, and secretion of cytokines, all processes which contribute to regional pain at the site of inflammation/injury (Figure 1).[1] It would be expected that the inherently destructive

[1] Unless otherwise stated, all figures contained herein are microphotographs of explanted Prolene polypropylene-based mesh material analyzed by me in my role as an expert witness on behalf of the plaintiffs and are used solely for the purpose of demonstrating the morphological features of explanted mesh

nature of the acute inflammatory response would need controls to minimize the extent of tissue damage. Generally, the degree of inflammation declines as the mediators of inflammation have short half-lives and are degraded after being released. However, in the case of a persistent stimulus, such as a non-absorbable mesh, in a compromised anatomic region, such as atrophic vaginal mucosal tissue, the ongoing contraction and migration of the foreign body can lead to continued tissue injury with associated clinical sequalae such as pain.

Chronic inflammation is considered to be an inflammatory reaction in which active inflammation, tissue destruction, and attempts at repair are occurring concurrently within a defined region. Like acute inflammation, there are numerous etiologies for chronic inflammation, again including prolonged exposure to potentially toxic endogenous or exogenous agents. An example of such an exogenous agent would be non-absorbable polypropylene mesh. In contrast to acute inflammation, which is manifested by various vascular changes and a predominantly neutrophilic infiltration, chronic inflammation is characterized by involvement by mononuclear cells, mainly lymphocytes and macrophages, and connective tissue replacement of damaged tissue. The macrophage is typically the dominant cell noted in the context of a chronic inflammatory reaction. Macrophages, once activated, like neutrophils, secrete a wide variety of biologically active products. However, in the case of macrophages, this cascade of events leads to the recruitment of other inflammatory cells, namely lymphocytes, which can ultimately result in tissue fibrosis. The bidirectional interaction of lymphocytes and macrophages together is characteristic of chronic inflammatory responses, as macrophages display foreign antigens to T lymphocytes, which ultimately stimulates T-cell responses. The chronic inflammatory response is typically the dominant type of local immune reaction seen in foreign body reactions, such as to synthetic mesh (Figure 2).

Granulomatous inflammation is a distinctive pattern of a chronic inflammatory reaction encountered in a limited number of immunologically mediated, infectious and non-infectious conditions. One type of granuloma, termed a foreign body granuloma, as the name implies develops when foreign material is introduced into the tissue and is large enough to preclude phagocytosis by a single macrophage. This reaction is often characterized by the presence of multinucleated giant cells, representative of fused epithelioid macrophages (Figures 3-5).

The chronic inflammatory response is closely intertwined with the process of repair. During repair, the injured tissue is replaced through regeneration of native parenchymal cells, by filling of the defect with fibrous tissue (scarring) or, most commonly, by a combination of these two processes. Tissue repair by fibrosis, though an attempt at healing with subsequent strengthening and repair of the tissue, may be harmful depending on the degree of collagen deposition and anatomic location in which it occurs.

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specimens which correlate to the pathological response to polypropylene mesh material described in the medical and scientific publications relied on by me in formulating my opinions.

In a broad sense, the term "fibrosis" applies to any abnormal deposition of connective tissue, though the degree of such deposition will determine the functional impairment, if any. When large defects are initially present, or in the case of some larger foreign bodies, a greater degree of granulation tissue is formed and subsequent wound contraction can occur. Fibrotic bridging is a histological phenomenon closely associated with the clinical consequence of mesh shrinkage. Fibrotic bridging refers to collagen deposition and inflammatory cell infiltration exceeding more than half of the pore size of the mesh (Klinge 2002) (Figures 6-11).

Similarly movement and shrinkage/kinking of the mesh may lead to migration towards nearby structures, ultimately causing fistulas, organ dysfunction, or even perforation (Figures 12-15). In contrast, more subtle histological features have also been shown to correlate with an increased sensation of pain. A study by Bendavid et al (2015) showed that mesh explants in patients complaining of pain contained a higher nerve density compared to tissue examined from patients who simply experienced a hernia recurrence. In this study, many of the nerves showed distortion and entrapment by the mesh material and fibrosis, while occasional areas resulted in the microscopic appearance of a marked neural proliferation, termed a "traumatic neuroma" (Figures 16-18). Therefore, in patients experiencing chronic pain and/or dyspareunia, studies showing significant resolution of symptoms following removal of the mesh (Firoozi 2012; Crosby 2014; Danford 2015), support the idea that nerve proliferation and entrapment by fibrosis/scaring between the mesh filaments as a likely etiology.

With respect to the histologic features that accompany these functional properties, an Ethicon scientist, Dr. Joerg Holste (2005) noted that such meshes lead to excessive scar plate formation, while others, including Dr. Klinge and colleagues, found that the degree and quality of the fibrosis was directly related to the amount of the inflammatory reaction and associated foreign body reaction at the interface between the mesh and the patient's tissue. These cellular responses result in subsequent restriction of the graft, leading to significant complications of chronic pain. In addition, it is clear from Ethicon's internal documents that its polypropylene mesh products are associated with considerable mesh contraction resulting from the fibrous stromal reaction in their surgical meshes containing polypropylene (ETH.MESH.01774758). When mesh contracts or shrinks, it can cause the patient to experience complications, including scarring and chronic pain. According to Ethicon's Medical Affairs Director, Piet Hinoul, who testified in 2013 in *Gross, et al vs Gynecare et al,* complications associated with its Prolift device include histological findings of a significantly scarred vagina with life-long risk of erosion, mesh contraction resulting in severe, chronic pain, and the presence of a severe, chronic inflammatory reaction to the mesh material in some patients resulting in the formation of a scar plate and/or bridging fibrosis. According to Ethicon's internal documents there is "significant evidence that the complications associated with synthetic meshes can cause significant morbidity including infection, erosion, exposure, and pain"

In a 2007 presentation prepared by Ethicon's Research and Development (R&D) department, it was concluded that for an ideal vaginal mesh to not ultimately result in a negative sexual impact for the patient, the graft material would ideally be lightweight and with a large pore size (ETH.MESH.01218361-01218367). With respect to the use of this product in the vaginal floor, Ethicon's internal documents demonstrate that "the vaginal tissue to be augmented is often structurally compromised, atrophic, and devascularized. Such poor tissue quality increased the risk of poor tissue incorporation into the mesh potentially resulting in suboptimal healing and mesh exposure or erosion into an adjacent viscous." This was further verified in 2008 by Dr. Klosterhalfen, the Head of the Duren Institute who was hired as an outside pathology consultant for Ethicon, who summarized his microscopic findings in these cases by noting that the "foreign body tissue reaction followed by secondary fibrosis seems to play a special role in pelvic floor repair" (ETH.MESH.00006636). He actually had informed Ethicon two years prior (2006) that, also based on his studies, the foreign body reaction to these meshes can occur for up to 20 years (ETH.MESH.00870466). Additionally in 2008, he went on to state that this inflammatory reaction is important "because soft tissue coverage is thin in pelvic floor repair" and "fibrosis and folding in this area induce mesh erosions and ulcerations." In a following report delivered the next year, Dr. Klosterhalfen reported, following his histological evaluation of an additional 172 prolapse mesh specimens, that "fibrosis inevitably leads to mechanical irritation, particularly when wrinkling occurs, and should be seen as the basic cause of mesh-induced erosion and ulceration," leading to a setting in which "infection is commonly observed following erosion in the vaginal mucosa" (ETH.MESH.02157879-02157880). Ethicon's documents demonstrate that over the course of Dr. Klosterhalfen's interactions and meetings with Ethicon, he made numerous suggestions aimed at improving the biocompatible nature of mesh implants, including with regards to the choice and weight of the material used, the pore size, and the mechanical characteristics of the mesh products.

Finally, there are numerous publications and internal Ethicon documents that have demonstrated that polypropylene, including Ethicon's Prolene used to manufacture its SUI and POP mesh devices, undergoes *in vivo* degradation over time (Liebert 1976; Jongebloed 1986; Mary 1998; Costello 2007; Clave 2010; Wood 2013; ETH.MESH.15955438; ETH.MESH.1595540; ETH.MESH.15955463; ETH.MESH.13334286) (Figure 19). After implantation of polypropylene, the inflammatory response to the foreign body causes an oxidative burst of free radicals and peroxides leading to embrittlement, crack formation, and loss of mechanical properties (Mary 1998). It has also been found that cholesterol and esterified fatty acids can diffuse into the amorphous zones of polypropylene and impact its physical and mechanical properties, causing damage to the surface (Clave 2010). In many cases, within the cracked and degraded surface layer, blue synthetic granules consistent with a blue pigment that Ethicon adds to the polypropylene resin during the manufacturing process to color some of the mesh fibers blue to aid in visibility can be seen. This finding rules out the possibility that the cracked surface layer is biological, a conclusion which was reached by Ethicon's own scientists in 1984 who used polarization light microscopy

(ETH.MESH.15955462). Surface degradation of the polypropylene, including Ethicon's Prolene-based mesh devices, causes the device to become brittle and crack. This phenomenon increases the inflammatory and foreign body reaction and is a contributing cause of the complications experienced by patients (Mary 1998; Clave 2010).

SUMMARY OF OPINIONS:

1. Prolene Polypropylene surgical mesh, including that contained within many of Ethicon's stress urinary incontinence (SUI) and pelvic organ prolapse (POP) mesh devices, elicits a chronic foreign body inflammatory reaction in tissue;
2. Certain design features of polypropylene surgical mesh lead to scar bridging between polypropylene fibers and scar plating with encapsulation;
3. During repair of the tissue damaged by placement of the mesh device, the wound site contracts and shrinks the implant area;
4. Bridging fibrosis, scar plating/encapsulation, and shrinkage lead to a hardened, rigid device that is damaging to the surrounding vaginal mucosa;
5. Ethicon's Prolene-based meshes degrade and crack *in vivo* contributing to the inflammatory and foreign body reaction and associated complications;
6. The foreign body inflammatory reaction and resultant scarring and mesh contraction can lead to mesh-related complications like nerve entrapment (pain), erosion and extrusion, sexual pain, and urinary/bowel dysfunction.

FIGURES

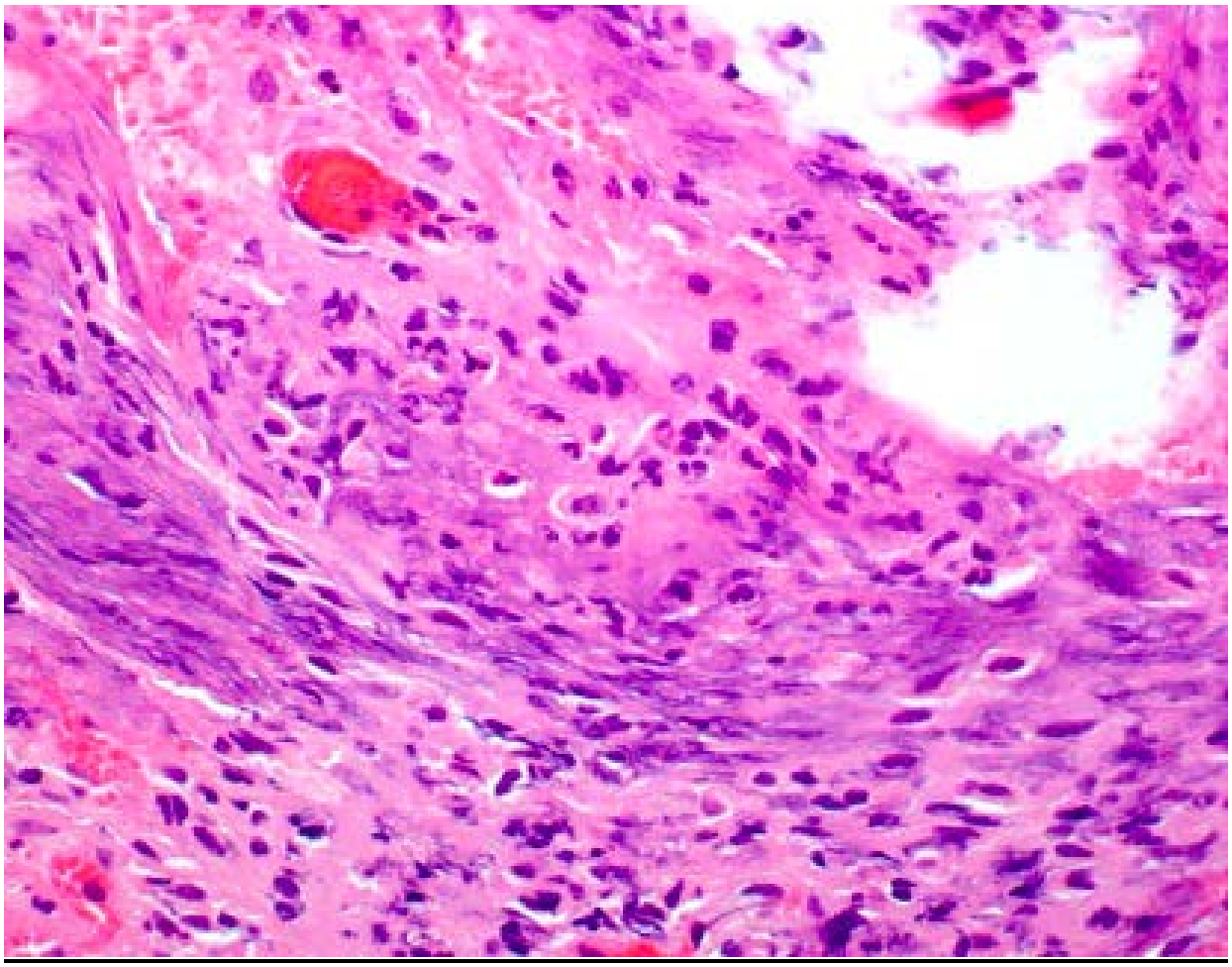

Figure 1: H&E histological specimen explanted from Plaintiff "MM" demonstrating acute inflammation present in areas associated with the mesh and fibrosis, characterized by increased numbers of neutrophils in the stromal tissue (400x magnification).

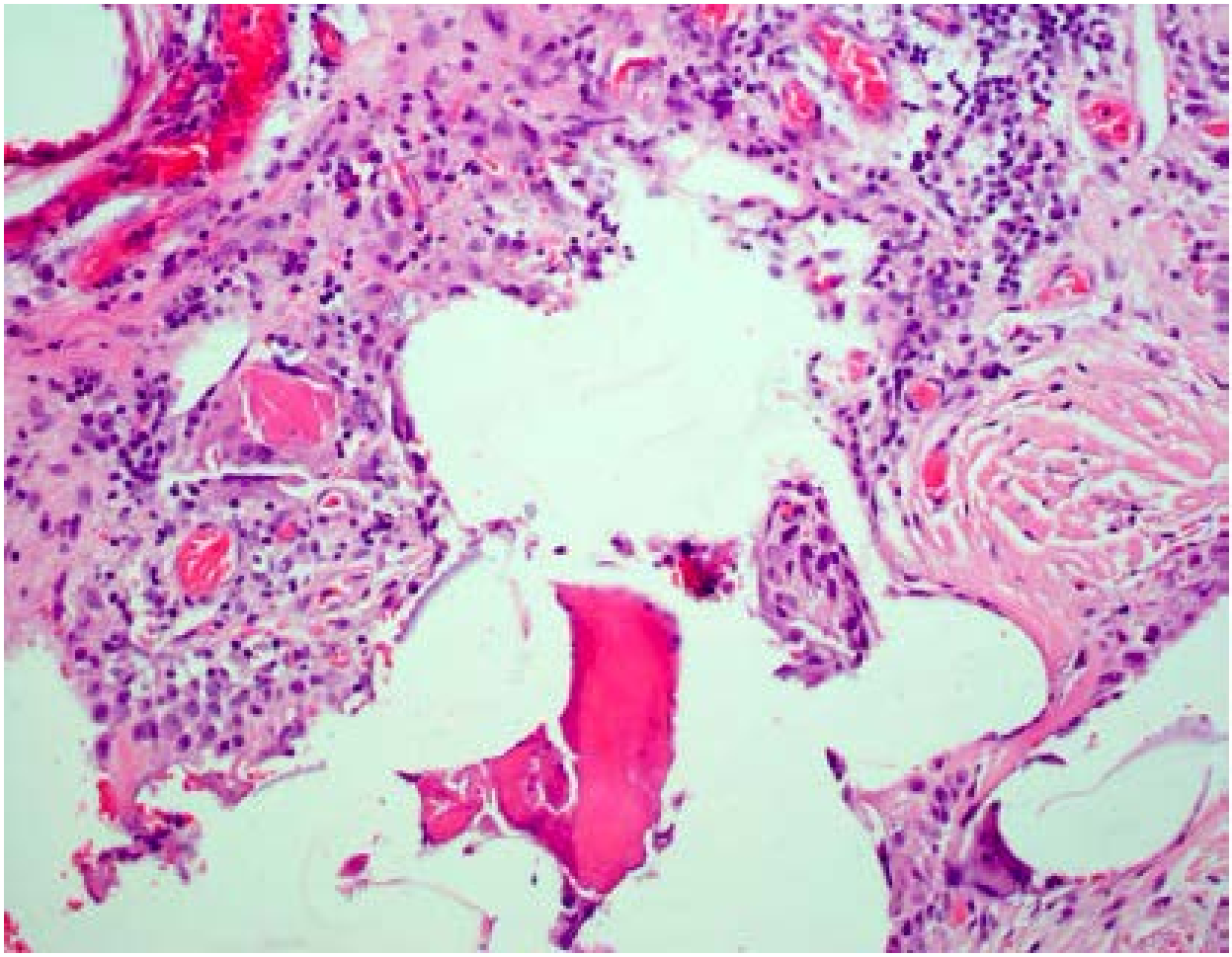

Figure 2: Mesh explanted from Plaintiff "MM" showing mesh filaments surrounded by a prominent chronic inflammatory infiltrate composed predominately by lymphocytes and macrophages with some congested blood vessels (200x magnification).

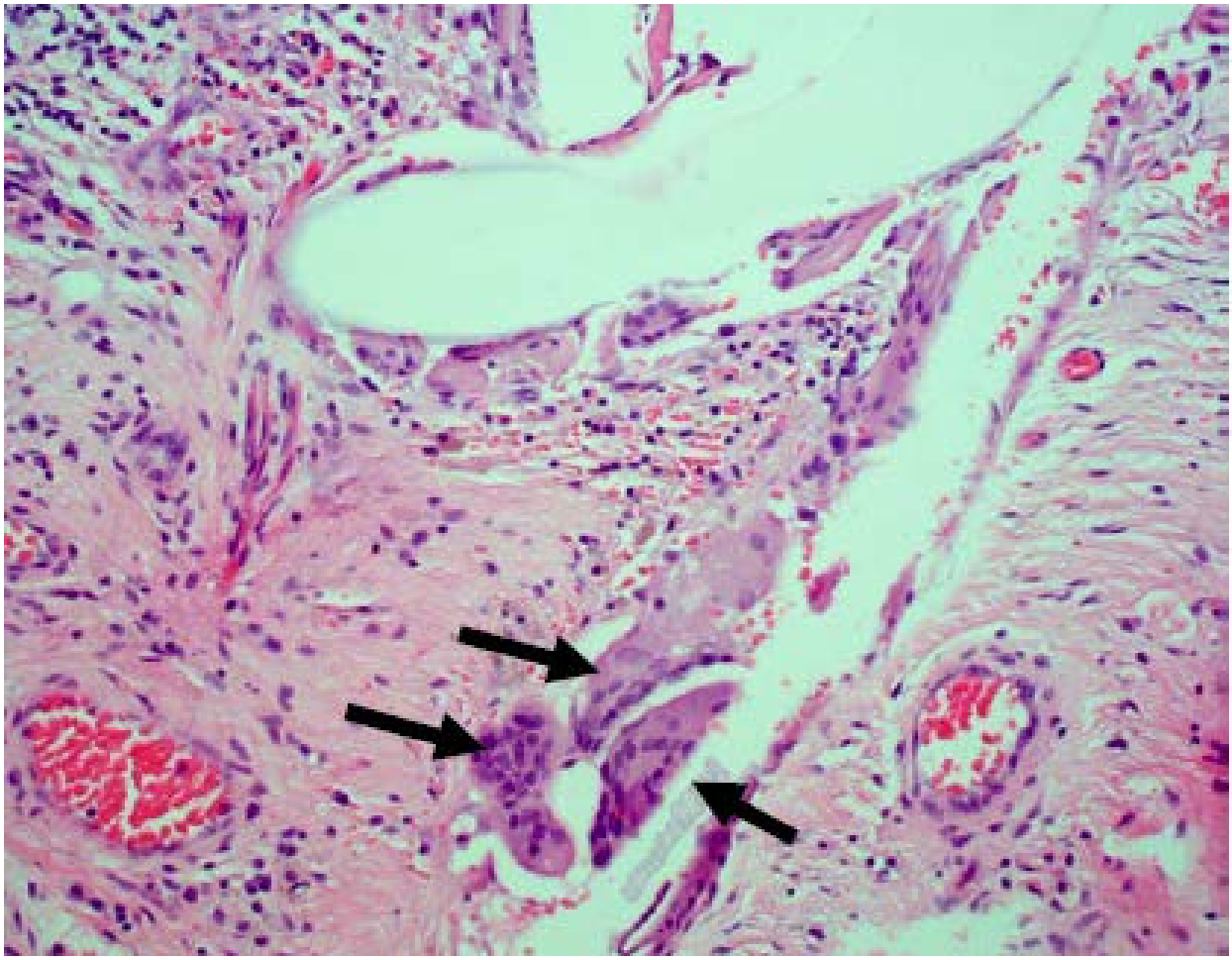

Figure 3: H&E of mesh explanted from Plaintiff "MM" showing vaginal mesh filaments surrounded by numerous, large foreign body multinucleated giant cells (macrophages) with chronic inflammation and dilated blood vessels (200x magnification).

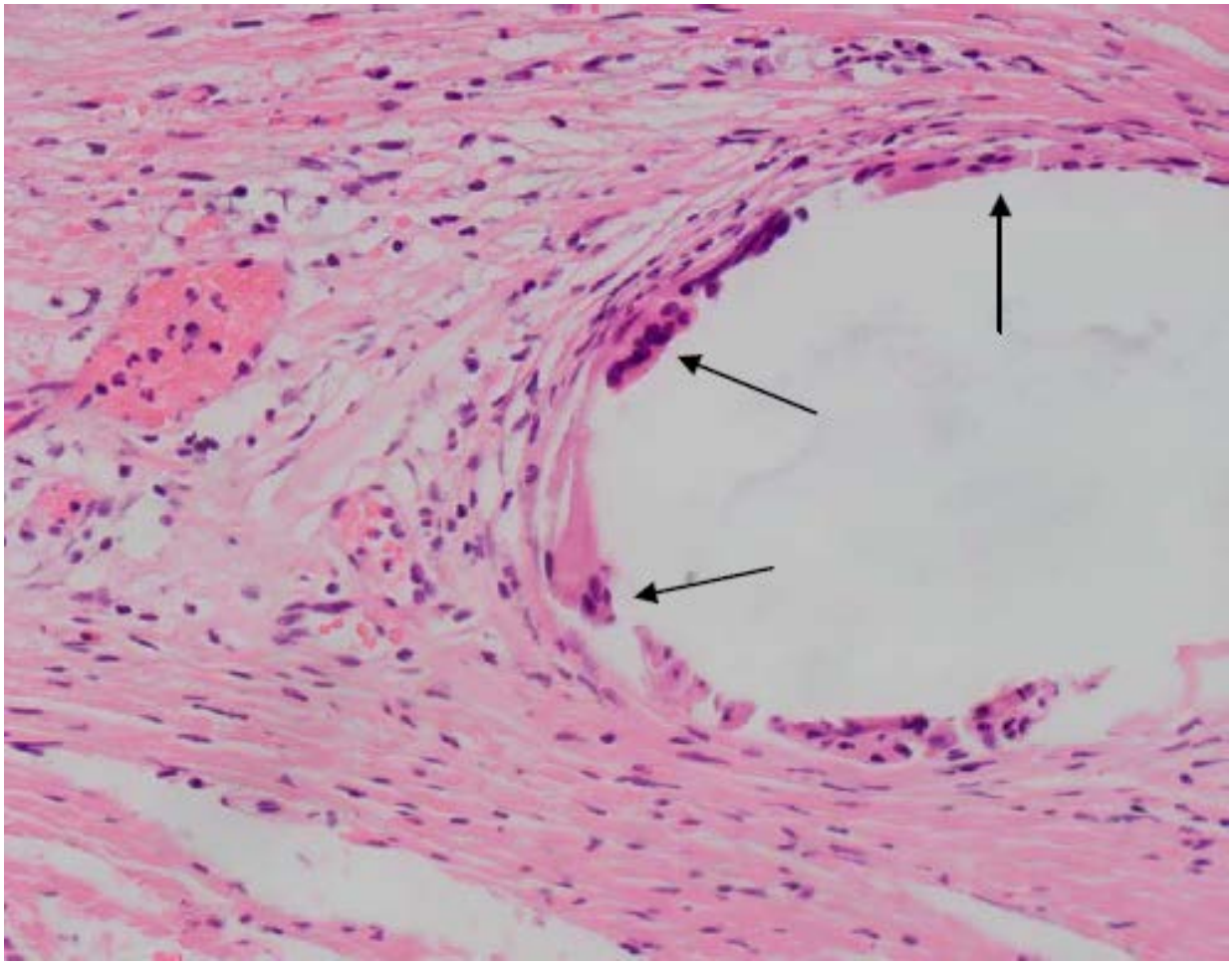

Figure 4: H&E of mesh explanted from Plaintiff "SC" demonstrating foreign body multinucleated giant cells (arrows) surrounded mesh filaments and is accompanied by a chronic inflammatory tissue reaction (400x magnification).

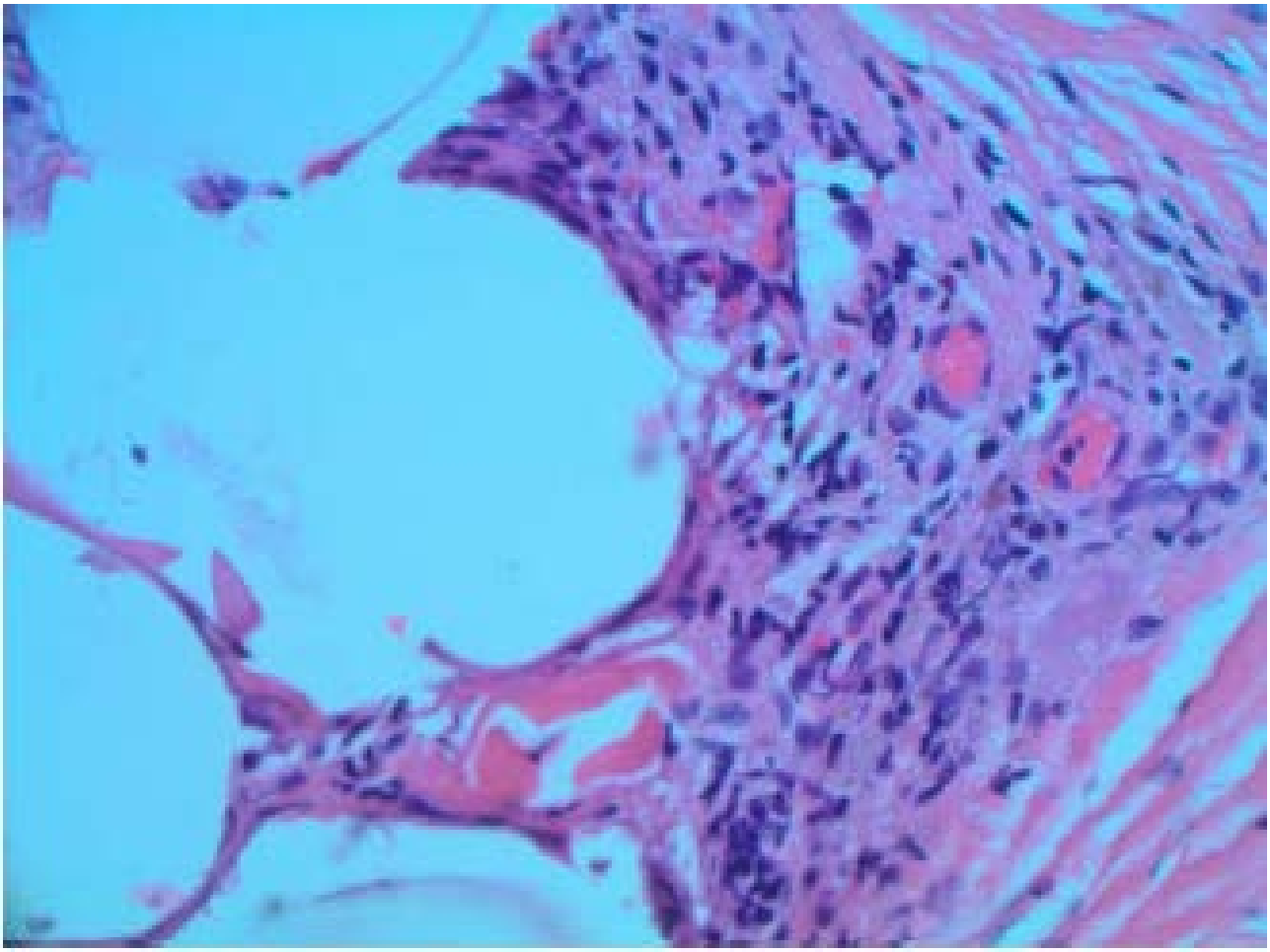

Figure 5: H&E of mesh explanted from Plaintiff "TC" demonstrating granulomatous tissue reaction associated with adjacent mesh filaments (400x magnification).

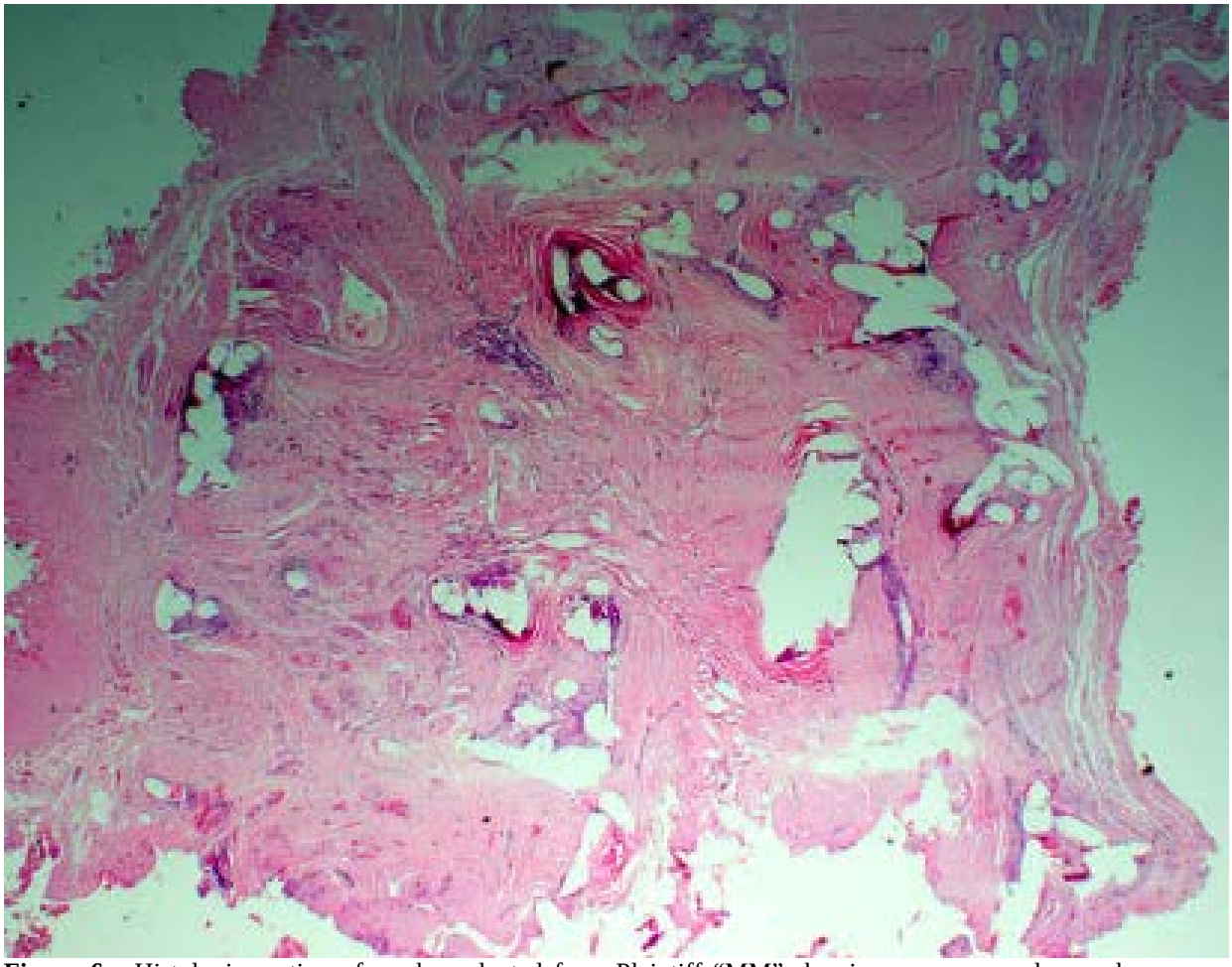

Figure 6: Histologic section of mesh explanted from Plaintiff "MM" showing numerous polypropylene filaments, each surrounded by foreign body granulomas and chronic inflammation, separated by dense areas of fibrosis without intervening adipose tissue ("bridging fibrosis") (40x magnification).

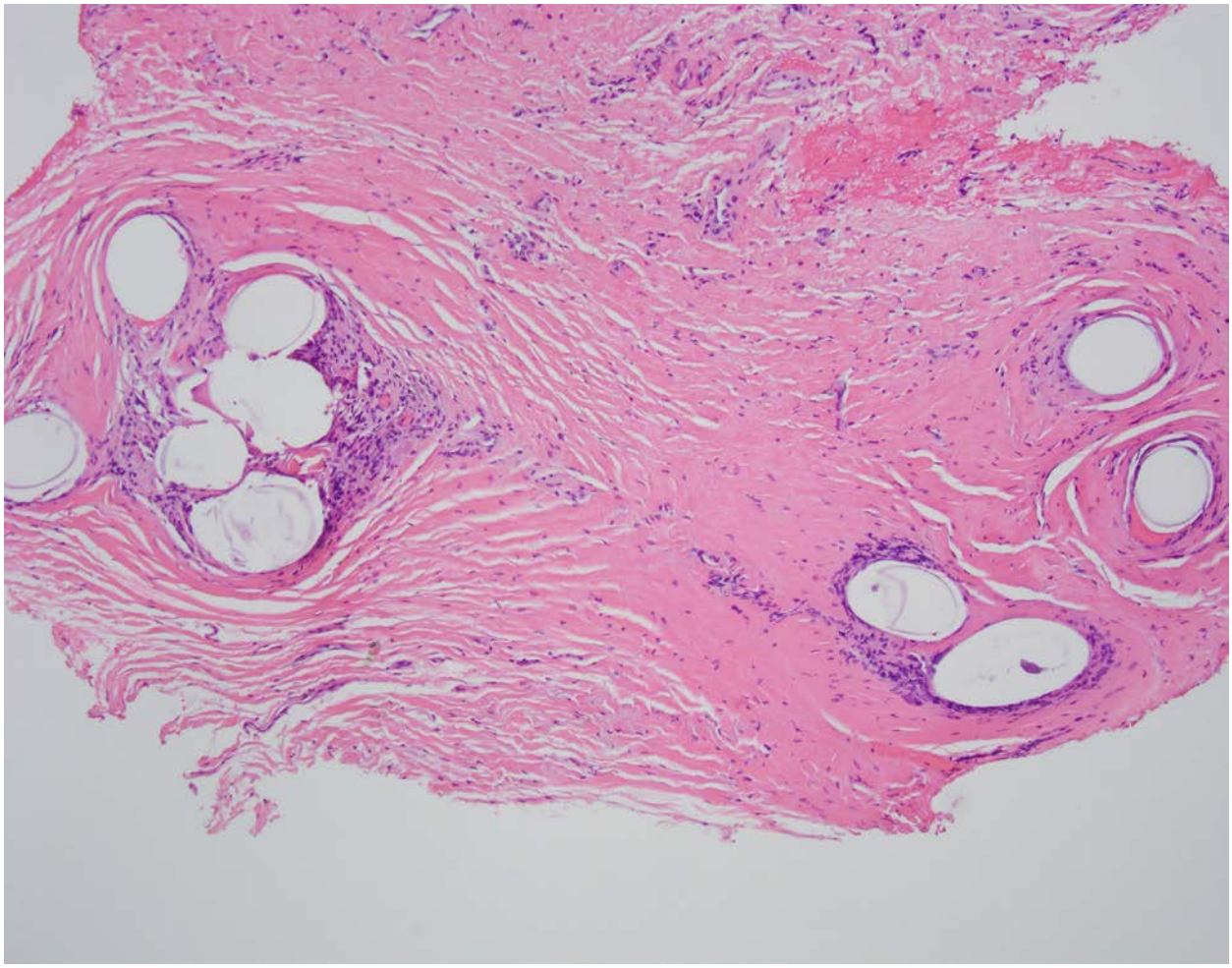

Figure 7: H&E of mesh explanted from Plaintiff "TC" showing bridging fibrosis separating areas of mesh filaments with chronic inflammation (100x magnification).

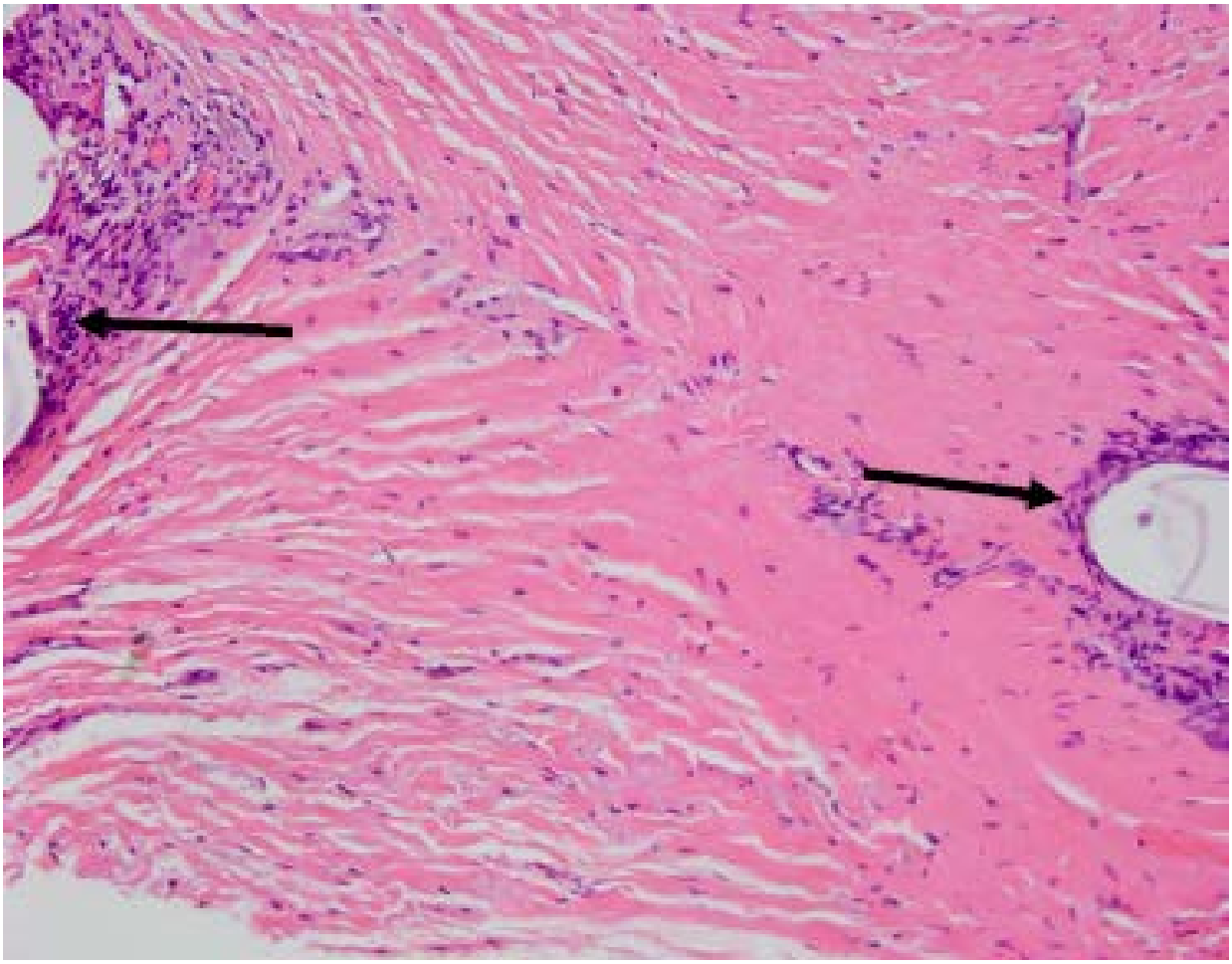

Figure 8: H&E of explanted mesh from Plaintiff "TC" showing prominent hypocellular and hyalinized fibrosis extending between mesh filaments (arrows) (200x magnification).

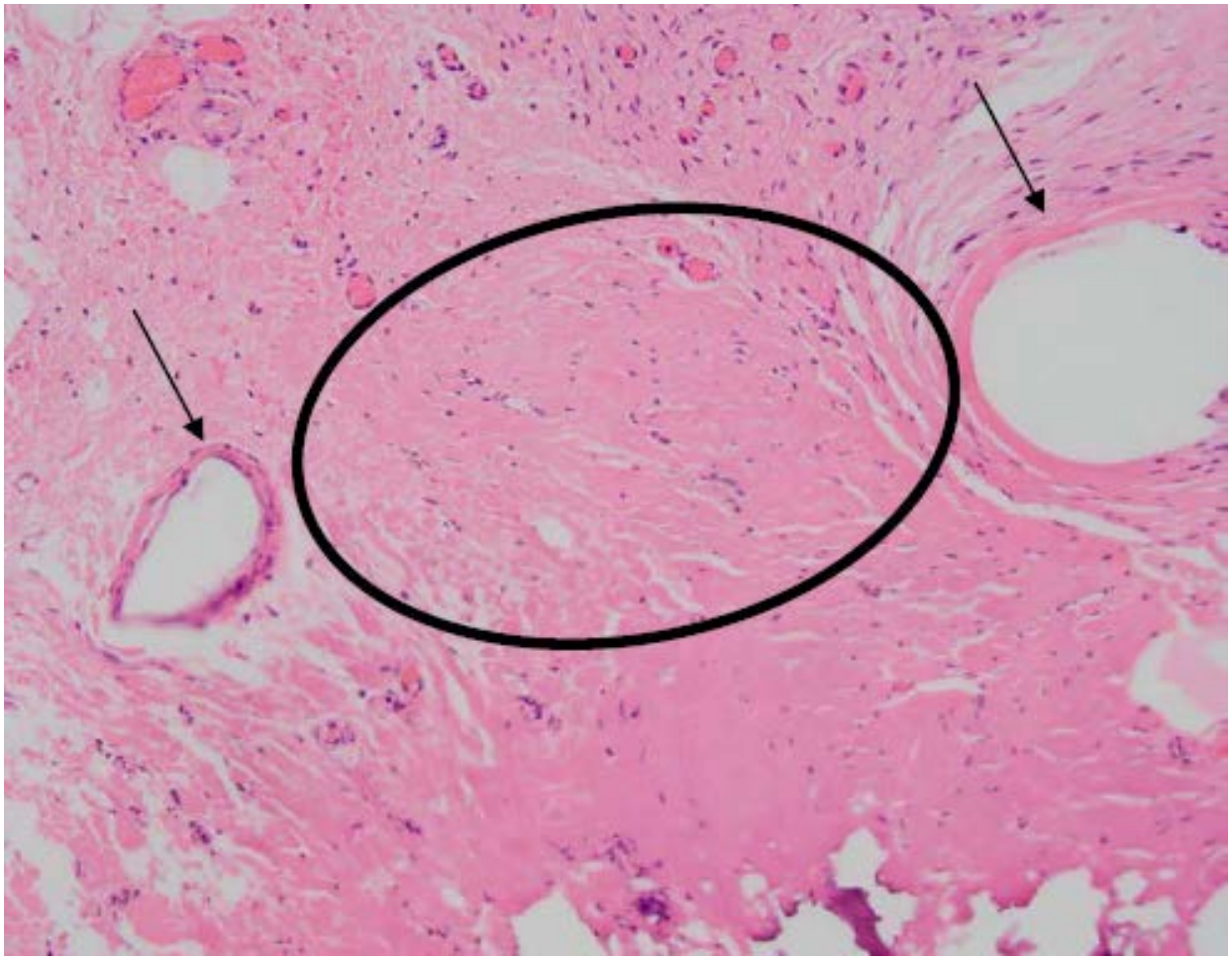

Figure 9: H&E of mesh specimen explanted from Plaintiff "SC" showing area of bridging fibrosis (circle) separating mesh filaments (arrows) (200x magnification).

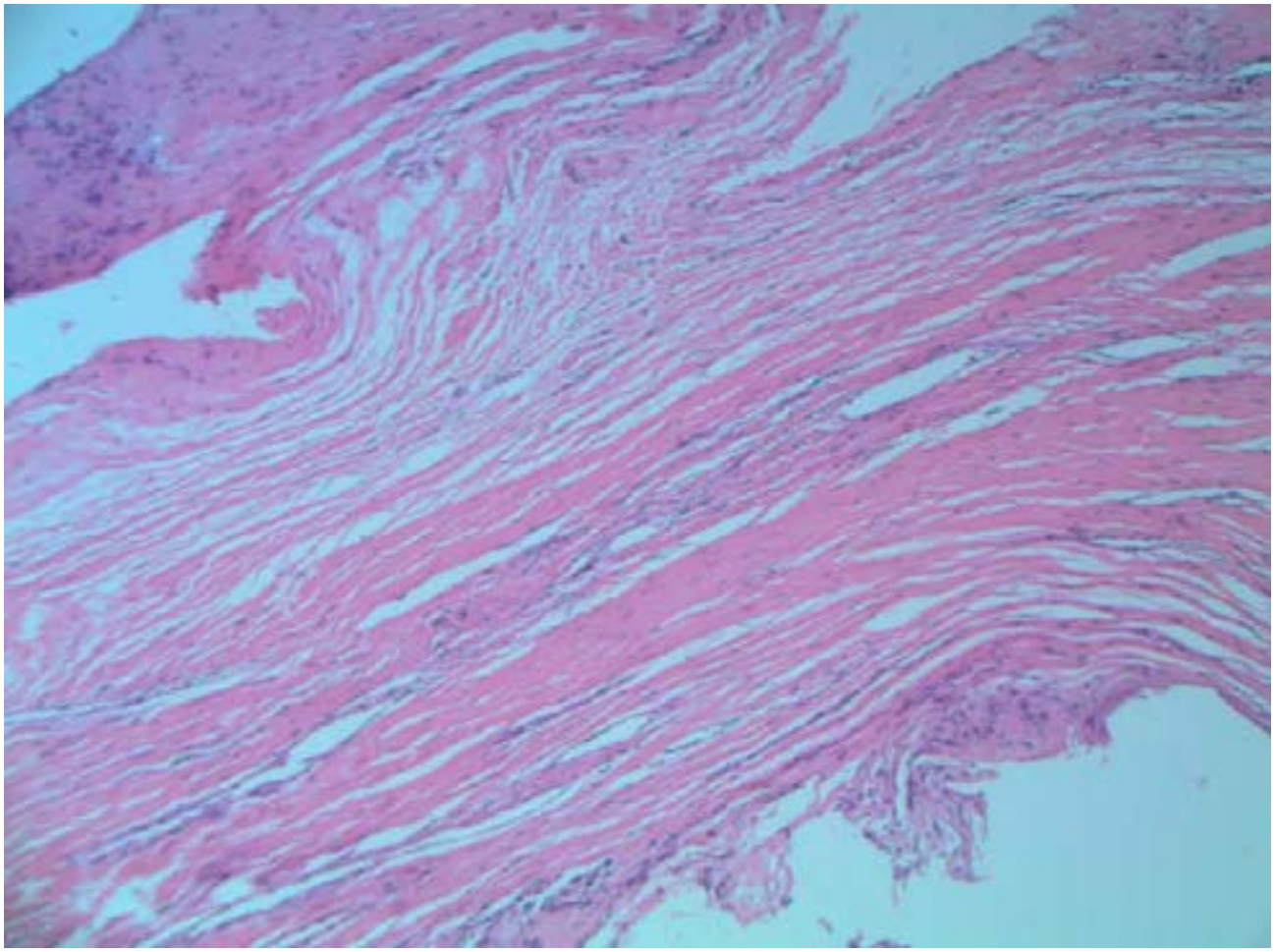

Figure 10: H&E of mesh explanted from Plaintiff "MS" showing bridging fibrosis separating two mesh filament spaces (200x magnification).

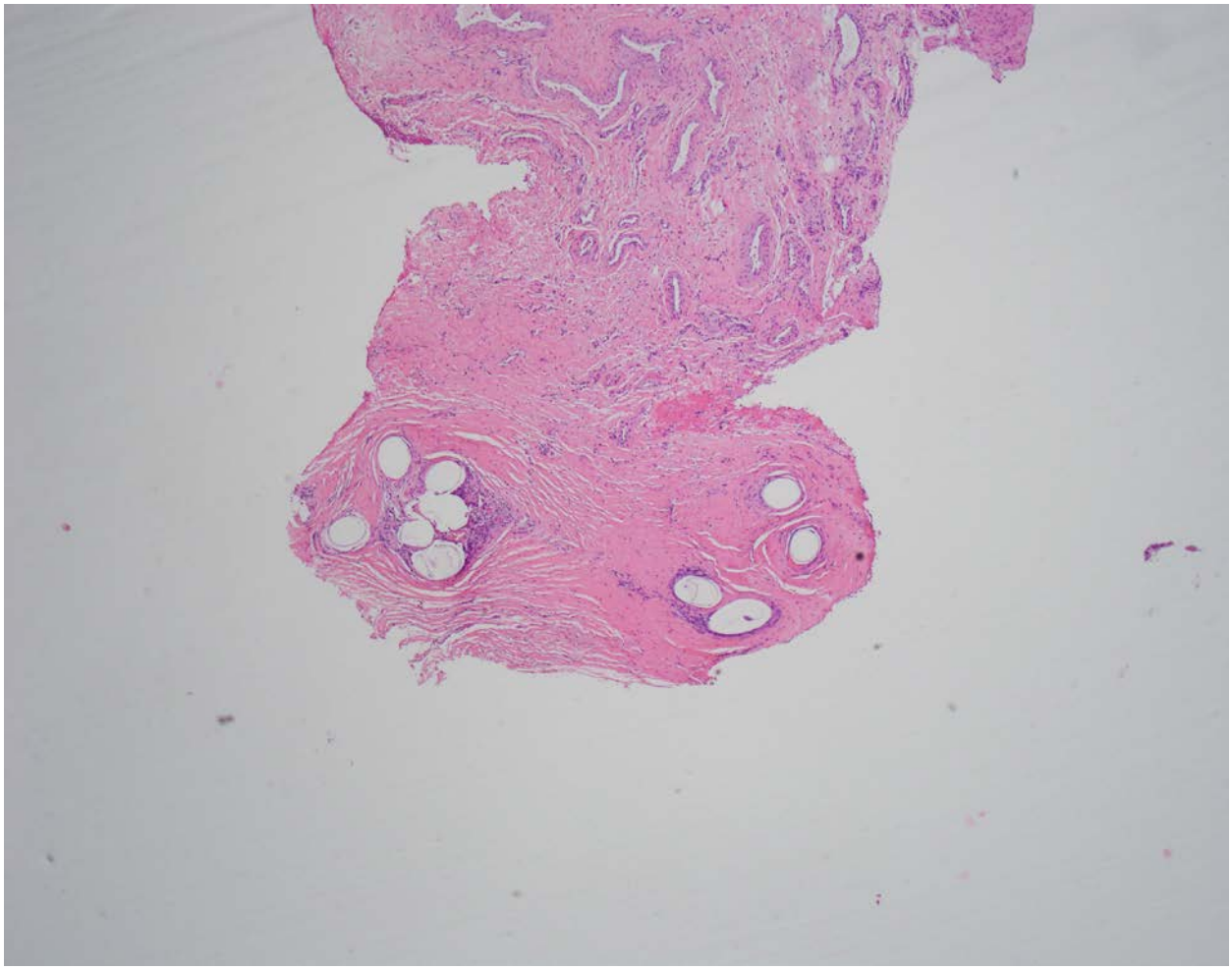

Figure 11: H&E of mesh explanted from Plaintiff "TC" showing encapsulating fibrosis ("scar plate") surrounding mesh filaments (40x magnification).

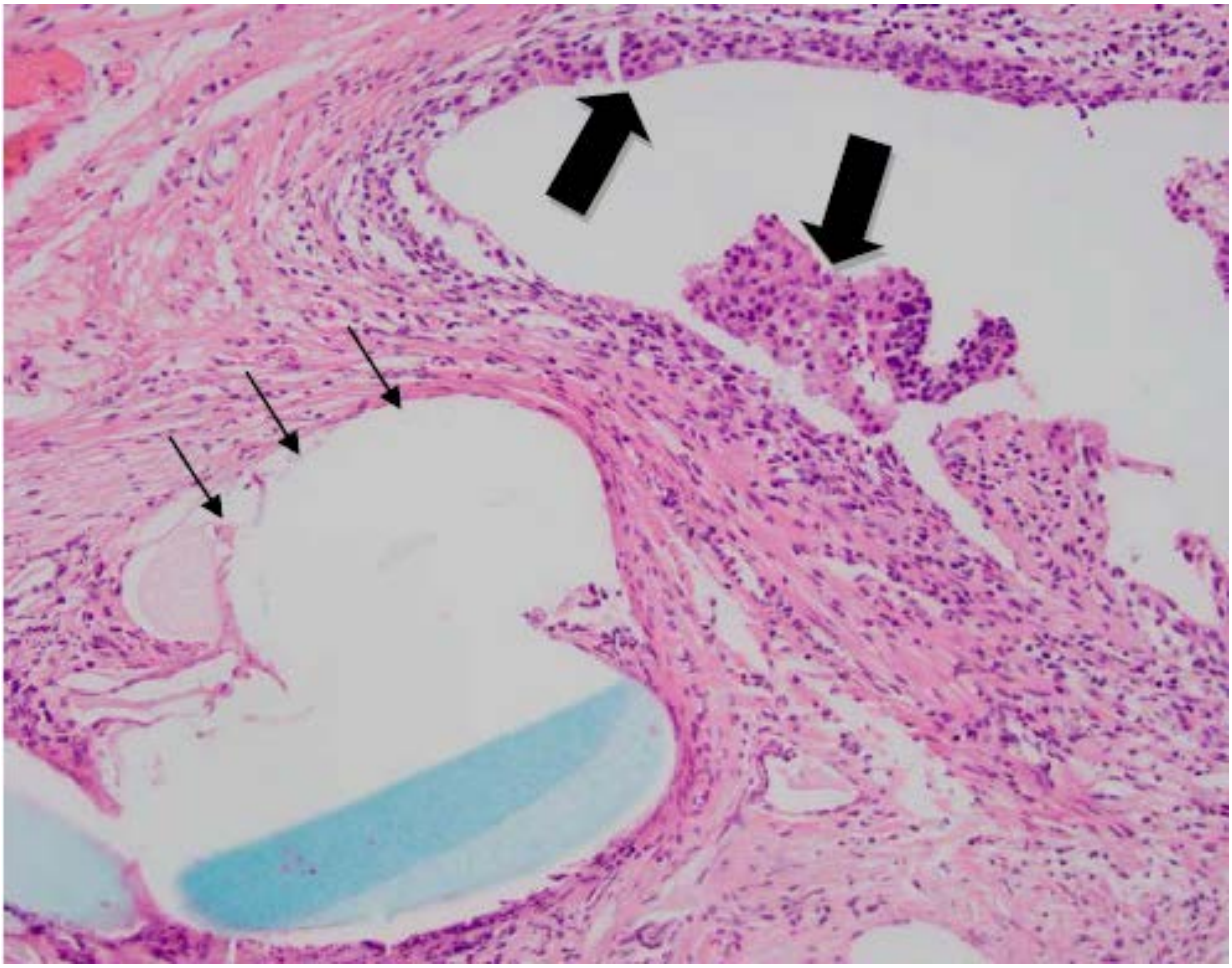

Figure 12: H&E of mesh explanted from Plaintiff "SC" showing mesh filaments (thin arrows) with associated perifilamentous fibrosis and chronic inflammation, eroding through the urothelial lining (block arrows) (200x magnification).

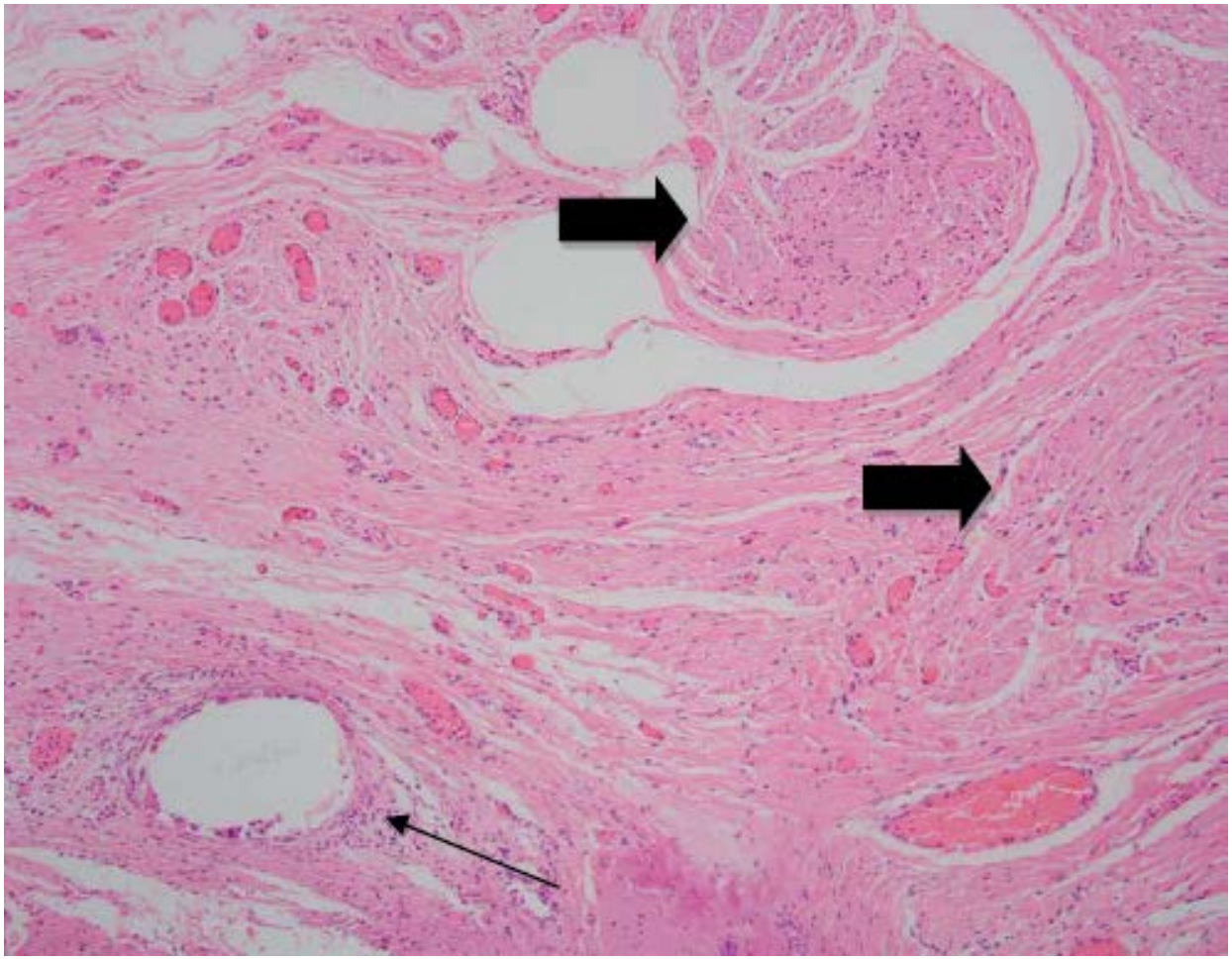

Figure 13: Histological section of mesh explanted from Plaintiff "SC" showing mesh filament (thin arrow) with associated perifilamentous fibrosis and chronic inflammation, involving the bladder smooth muscle bundles (block arrows) (100x magnification).

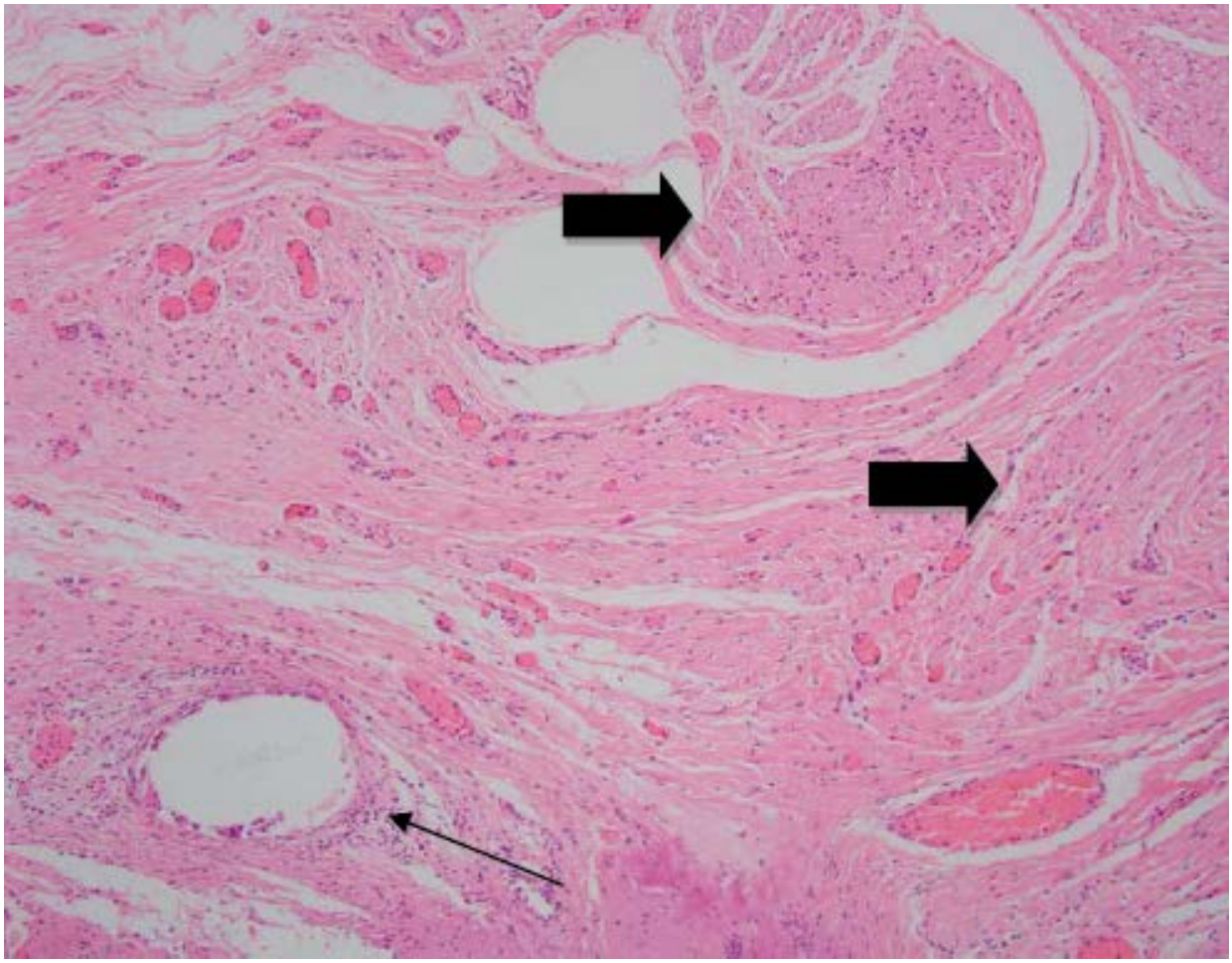

Figure 14: H&E of mesh explanted from Plaintiff "SC" showing mesh filament (thin arrow) with associated perifilamentous fibrosis and chronic inflammation, involving the bladder smooth muscle bundles (block arrows) (100x magnification).

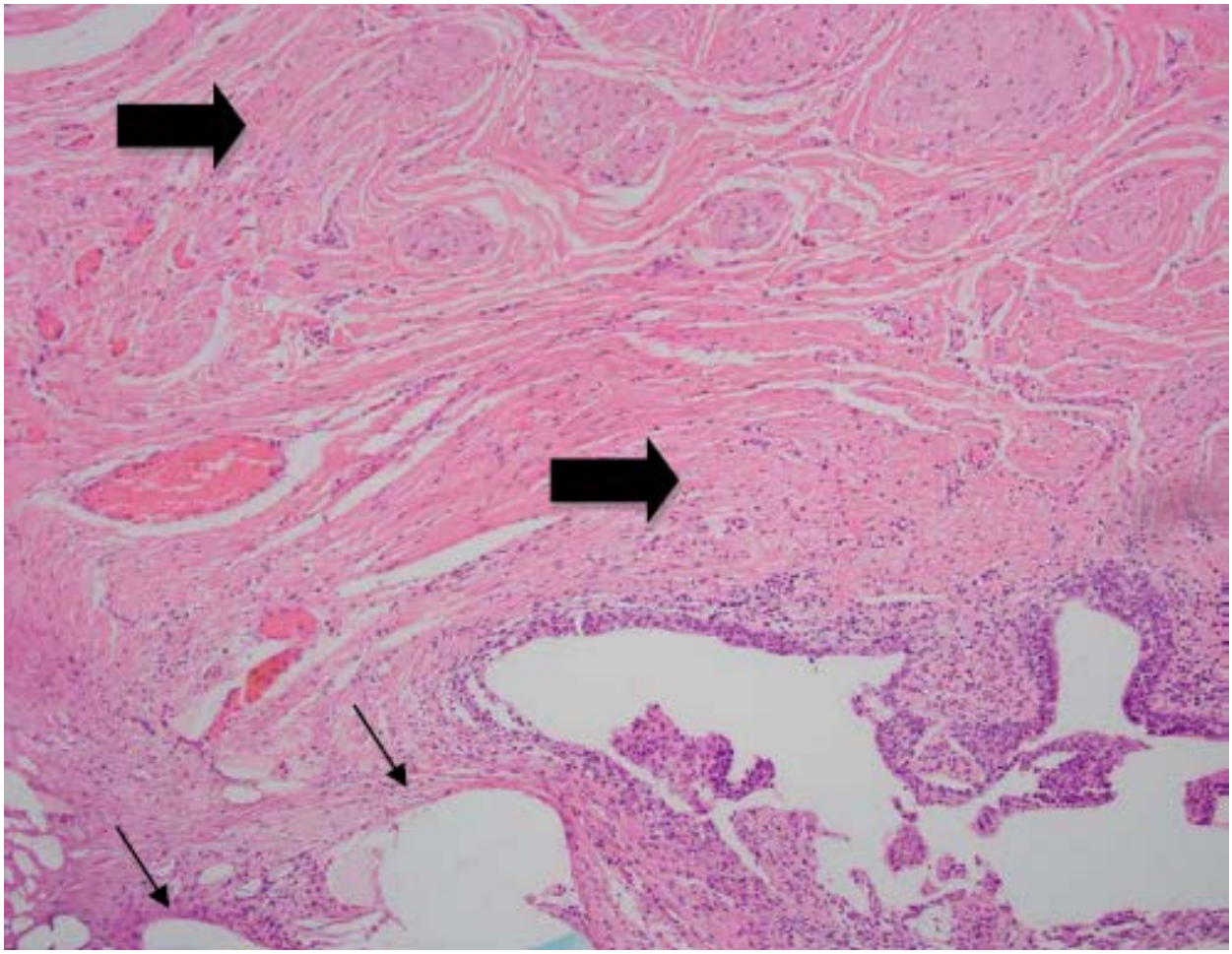

Figure 15: Another histology section of mesh explanted from Plaintiff "SC" showing mesh filaments (thin arrows) eroding into the urothelium with associated perifilamentous fibrosis and chronic inflammation, involving the bladder smooth muscle bundles (block arrows) (100x magnification).

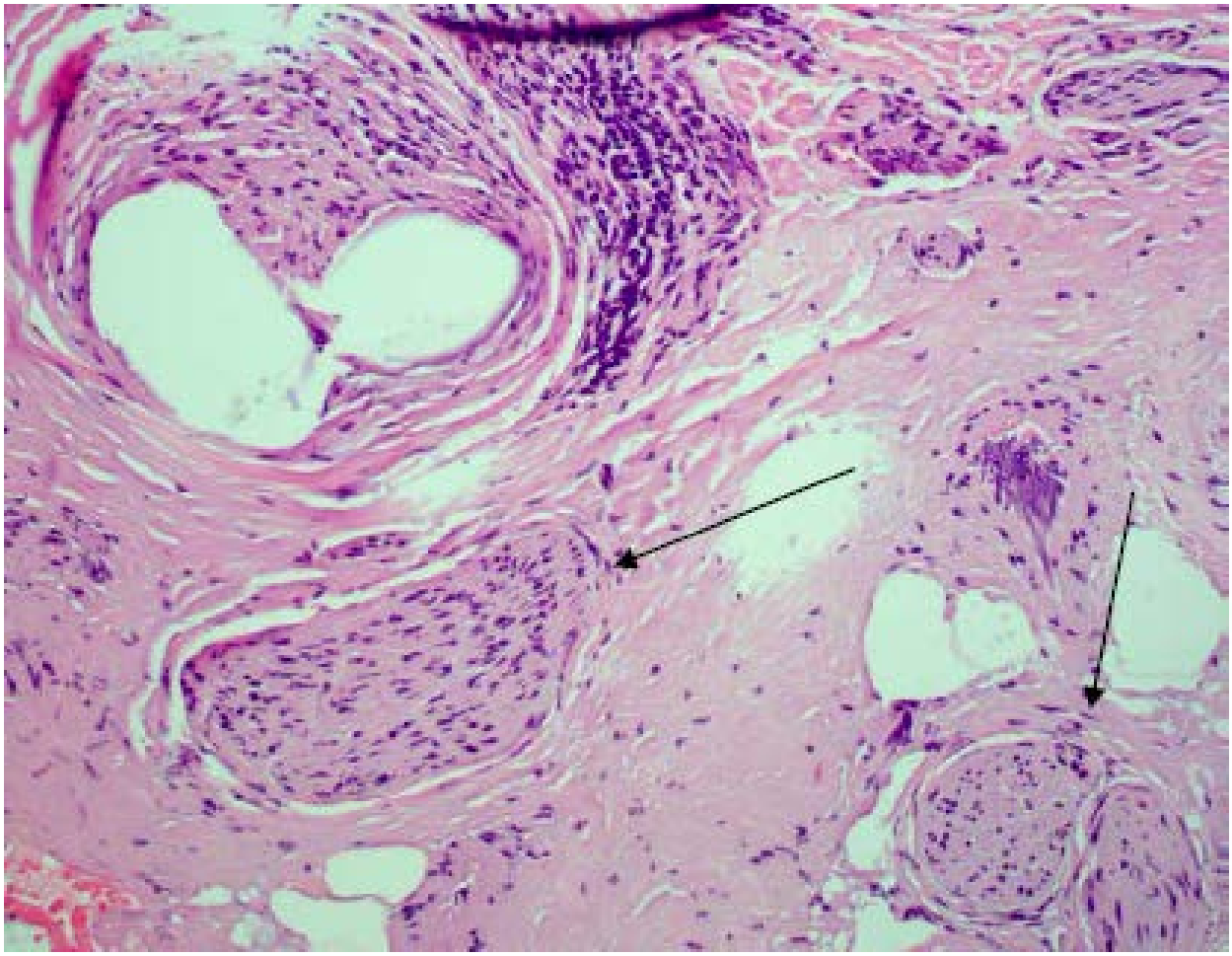

Figure 16: H&E stain of mesh specimen explanted from Plaintiff "MM" in which the prominence of the nerves (arrows) is evident without immunohistochemical stains, each surrounded by scar fibrosis (200x magnification).

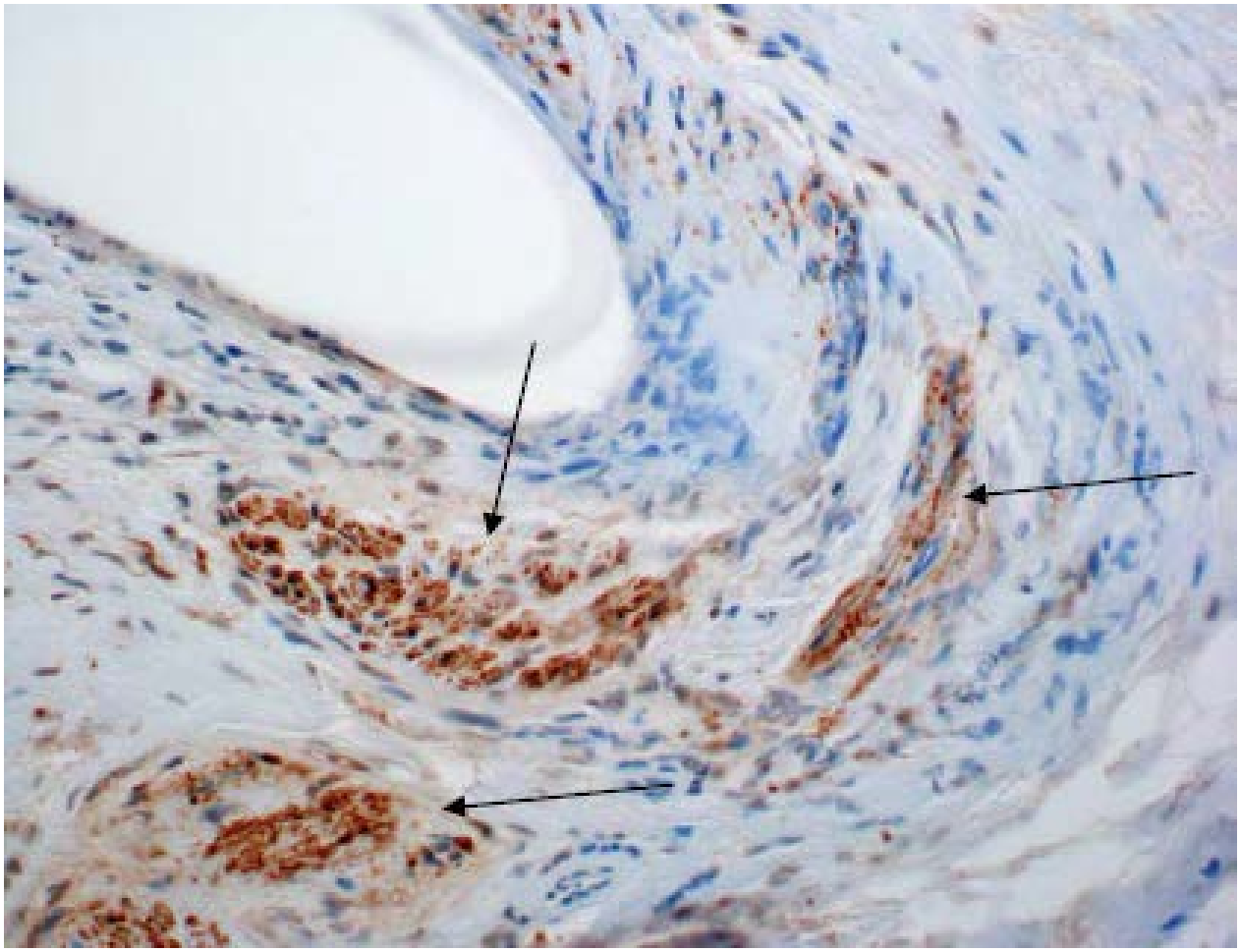

Figure 17: S100 stain of mesh explanted from Plaintiff "MM" highlighting the numerous, brown-staining nerves (arrow) that surround a large mesh filament and appear distorted and compressed by the associated inflammatory and fibrous response (400x magnification).

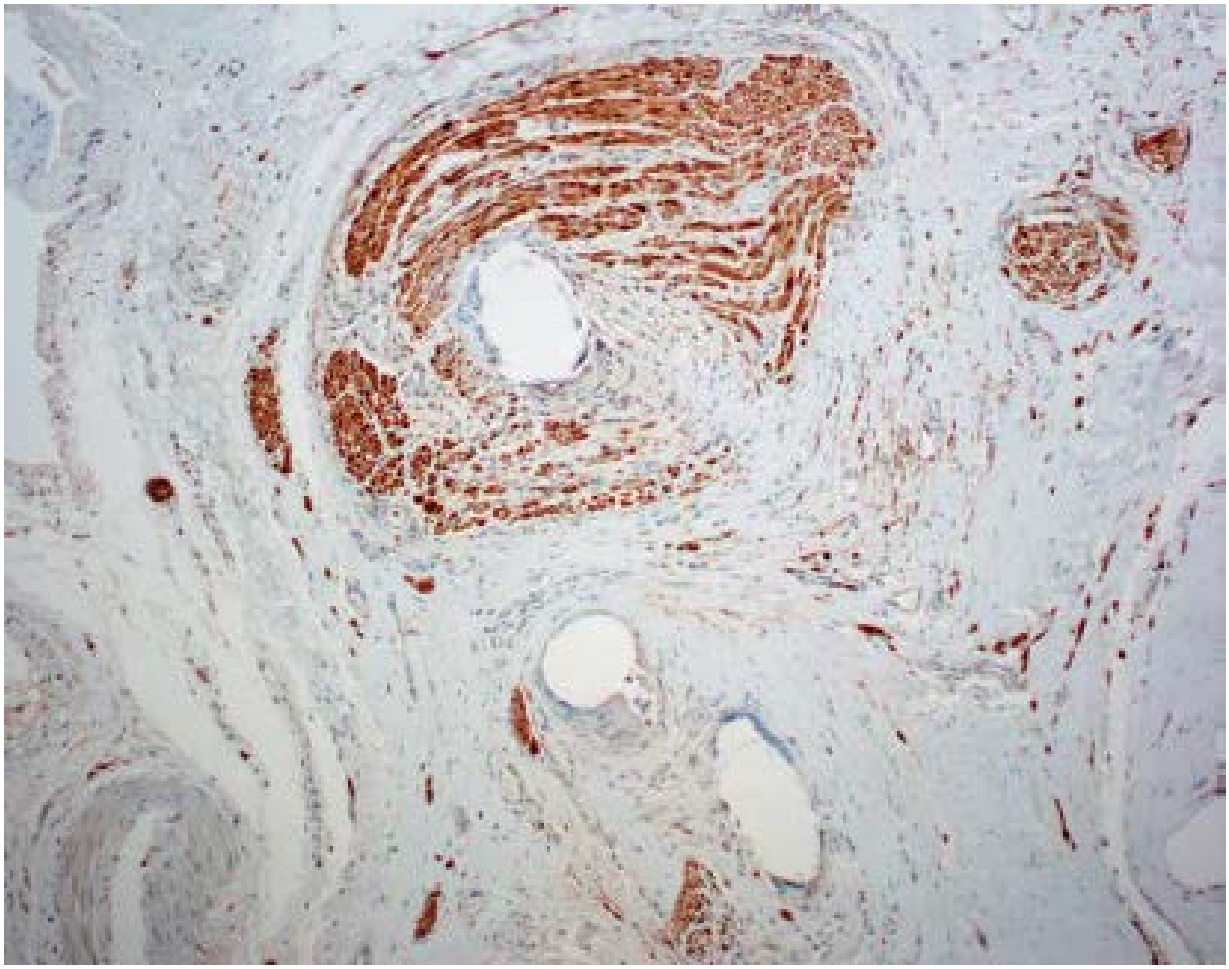

Figure 18: An S100 stain of mesh specimen explanted from Plaintiff "MM" highlighting the prominent and hyperplastic neural proliferation associated with a mesh filament, consistent with a "traumatic neuroma" (100x magnification).

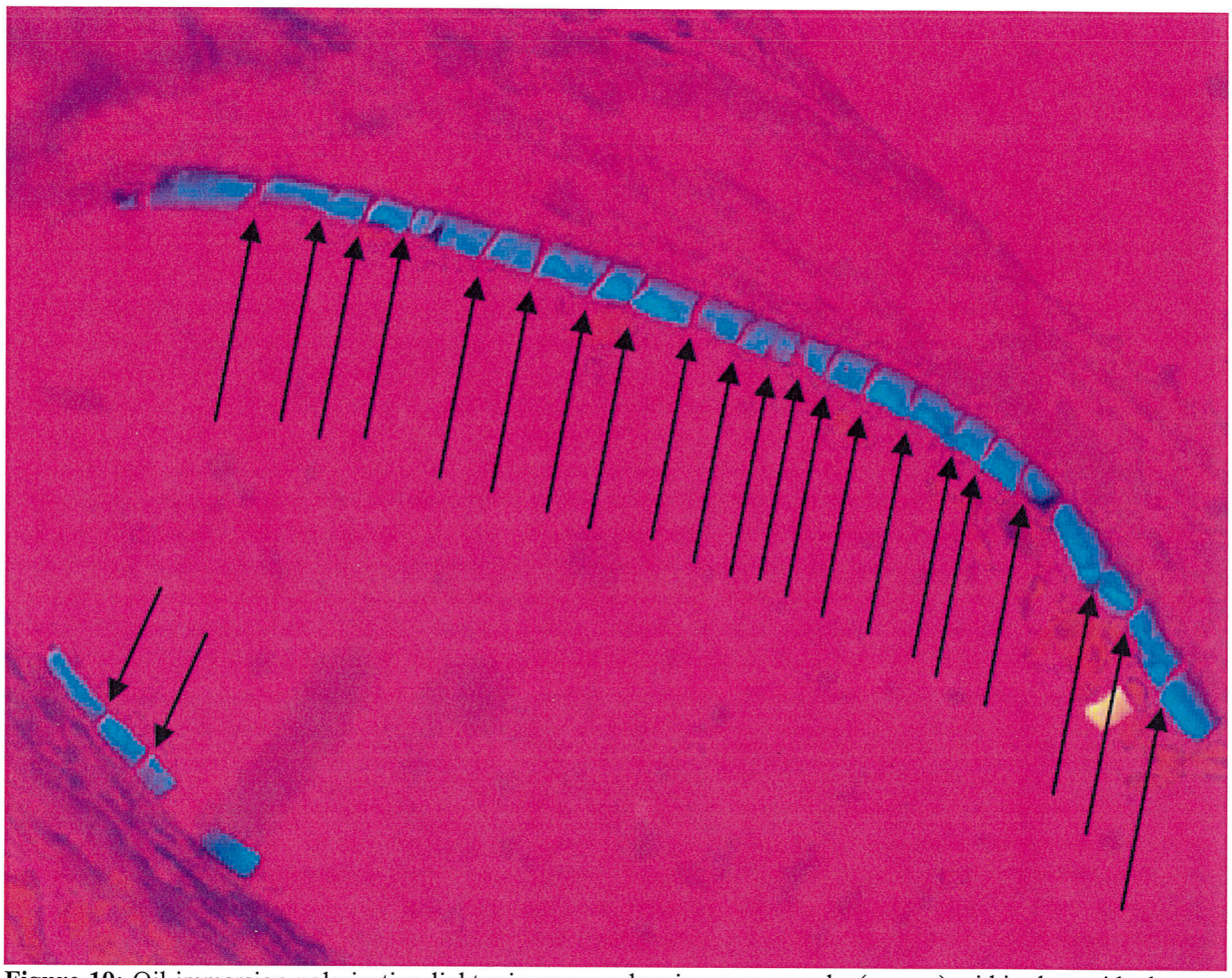

Figure 19: Oil immersion polarization light microscopy showing many cracks (arrows) within the residual polypropylene bark (1000x magnification) of mesh explanted from Plaintiff "TH".

7/1/2016
DATE

Paul J. Michaels, M.D